REMARKS

Claims 1-26 are currently pending in the application, while claims 15-20 and 22-26 are withdrawn from consideration. No new matter is added.

Priority

The Examiner stated that the Applicants have not filed copies of the British priority applications as required by 35 U.S.C. 119(b). Filed herewith are the British priority documents in compliance with 35 U.S.C. 119(b).

Oath/Declaration

The Examiner asserted that the oath or declaration was defective because non-initialed and/or non-dated alterations were made to the document. The Applicants herewith submit a newly executed oath/declaration in compliance with 37 CFR 1.67(a).

Rejection of Claims 1-14 and 21 Under 35 U.S.C. §112, First Paragraph

Claims 1-14 and 21 are rejected under 35 U.S.C. §112, first paragraph, for alleged lack of enablement.

The Examiner states at page 5 of the office action that "the specification fails to provide any relevant teachings or specific guidance which enable the claimed methods of controlling population of target insects." In view of the lack of guidance provided by the specification it would have required undue experimentation to use make and use the invention as claimed".

The Examiner further states on page 5 of the office action that:

> The claimed methods are unpredictable and undeveloped for controlling an insect population. . . However, the goal of the instant invention according to the specification (see page 13) is to release transgenic insects into wild-type insect populations. The transgene is transmitted through breeding into a wild-type population to produce target populations of insects susceptible to a pro-drug or pro-insecticide.

The Examiner also states on pages 5 through 6 of the office action that:

> The instant invention appears to be unpredictable and undeveloped in light of Markaki et al (Insect Biochemistry and Molecular Biology, 2004, 34: 131-137), which discusses the claimed invention and its limitations. Markaki et al suggest the CD/5-FC/Yp1 promoter system is unsuitable for large-scale applications due to delayed action, high cost of 5-FC, and observed sensitivity of non-transgenic males. . . . The instant specification has not provided working examples or guidance with respect to use of other promoters in accordance with the claimed invention.

The Examiner further states on pages 6 through 7 of the office action that:

> With respect to conditional promoters, the hsp 70 promoter potentially could be used for developing sexing systems. However, the hsp 70 promoter has relatively low activity in non-Drosophilid insects as compared to that in *Drosophila*. See page 155. . . . In light of the above, it appears that appropriate sex-specific and/or conditional promoters are not readily available beyond Drosophila.

Applicants traverse the rejection on the grounds that the application as filed meets the enablement standard of teaching the ordinarily skilled artisan to practice the invention without undue experimentation.

Enablement

According to prevailing authority, enablement does not require Applicants to describe every potential embodiment encompassed by the claims, but rather requires that, after reviewing the application, the ordinarily skilled artisan be able to reproduce the claimed invention as claimed without resorting to "undue experimentation." In *In re Wands,* 858 F.2d 731, 8 U.S.P.Q.2d 1400 (Fed. Cir. 1988), the Federal Circuit defined undue experimentation as a conclusion reached after weighing many factual considerations including those cited in *In re Forman*, 230 U.S.P.Q. 546 at 547 (Pat. & Trademark Off. Bd. Pat. Inf. 1986) and relied upon by the Examiner:

(1) the quantity of experimentation necessary,

(2) the amount of direction or guidance presented,

(3) the presence or absence of working examples,

(4) the nature of the invention,

(5) the state of the prior art,

(6) the relative skill of those in the art,

(7) the predictability or the unpredictability of the art, and

(8) the breadth of the claims.

The court also stated that "[e]nablement is not precluded by the necessity for some experimentation such as routine screening. However, experimentation needed to practice the invention must not be undue experimentation. 'The key word is 'undue' not 'experimentation' ' " (citing *In re Angstadt*, 537 F. 2d 498 at 504, 190 U.S.P.Q. 214 at 219 (C.C.P.A. 1976)). The Court also stated that "the test is not merely quantitative, since a considerable amount of experimentation is permissible, if it is merely routine, or if the specification in question provides a reasonable amount of guidance with respect to the direction in which the experimentation should proceed." (citing *In re Jackson*, 217 U.S.P.Q. 804 at 807 (Bd. App. 1982)).

Furthermore, it is well settled that ". . . claims need not recite such factors where one of ordinary skill in the art, to whom the specification and claims are directed, would consider them obvious." *In re Skrivan, 166 U.S.P.Q. 85, 88 (C.C.P.A. 1970)* (reversing a final rejection for overbreadth of process claims, where the Examiner required applicant to insert limitations of operating conditions that were old and well-known in the art).

Furthermore, as stated by the Federal Circuit in *Engel Industries, Inc. v. Lockformer Co.* (946 F.2d 1526, 20 U.S.P.Q.2d 1300 (Fed. Cir. 1991)), "[t]he enablement requirement is met if the description enables any mode of making and using the claimed invention" (at 1304). MPEP § 2164.01(b) also addresses this issue, stating that "[a]s long as the specification discloses at least one method for making and using the claimed invention that bears a reasonable correlation to the entire scope of the claim, then the enablement requirement of 35 U.S.C. 112 is satisfied." (citing *In re Fisher*, 427 F.2d 833, 839, 166 U.S.P.Q. 18,24 (C.C.P.A. 1970). Applicants

respectfully submit that they have met the enablement requirement by disclosing at least one method for making and using the invention.

Applicants assert that the present application is enabled because the specification provides considerable direction and guidance for the claimed methods, as well as examples describing the claimed methods. Applicants submit further that the claimed invention is also enabled in view of what was known in the art as of the filing date of the application, as well as what is presented in post-filing publications.

The enablement requirement of 35 U.S.C. §112, first paragraph requires that the specification provide sufficient disclosure to permit one of skill in the art to practice the claimed invention without undue experimentation. Accordingly, under the claims of the present invention, the specification must teach one of skill in the art how to practice a method of controlling a population of insects by: (1) target insects comprising a gene encoding one constituent of an enzyme/pro-pesticide system under the control of a regulatory region which expresses the enzyme in a sex specific manner; (2) transforming target insects with the gene to allow spread within the population and (3) administering to the target insects the remaining constituents of the enzyme pro-pesticide system, wherein the enzyme catalyzes the conversion of the pro-pesticide to a pesticide.

Applicants assert that the present application is enabled because the specification provides considerable direction and guidance for the claimed methods, as well as examples describing the claimed methods. First, the specification teaches a gene encoding an enzyme/pro-pesticide system under the control of a regulatory region which expresses the enzyme in a sex specific manner. Example 2 teaches construction of a female-specific cytosine deaminase expression vector, to produce the transformation plasmid pCasper-YP-CD. Sex-specific expression was confirmed in *Drosophila melanogaster* by coupling the Yp1 promoter/enhancer to GFP. Similarly the application teaches at pages 19 to 20 that "15 Medfly transgenic genes have been generated using the same transposon. FIG.2 shows female-specific expression of GFP driven by the Drosophila YP promoter in one of these Medfly lines."

Second, the application teaches transforming target insects with a gene encoding the first constituent of an enzyme/pro-pesticide system which is then spread within a target insect population. For example, Example 3 on page 20, states:

> Transformation was performed using previously described methodology (Rubin and Spradling, 1982, Science 218, 348-353). Transformants were detected by screening the G1 progeny of the injected flies for expression of the dominant *white* marker present in pCasper-YP-CD.

Thus, Applicants teach transformation of target insects with pCasper-YP-CD, and spread of the gene within a target population of insects. Spread of the gene within the target population was confirmed by screening the G1 progeny for expression of the dominant white marker.

Third, the application teaches the administration of the remaining constituent of the enzyme pro-pesticide system, resulting in the conversion of the pro-pesticide to a pesticide. Example 7 teaches the administration of 5-FC to CD transformed flies. A substantial reduction in viability is observed in female CD flies compared to male CD flies in the presence of increasing concentrations of 5-FC. In view of the above, Applicants assert that the method of claims 1-14 and 22 are fully enabled.

The Examiner states that "the claimed methods are not enabled because they are unpredictable and undeveloped for controlling an insect population." The Examiner then states, that the goal of invention, according to the specification, is to release insects into wild-type insect populations.

Applicants submit that although the claims do not require that the "target insect population" be a wild-type insect population, or a population that is other than a laboratory population of insects, the application sufficiently teaches controlling a wild-type population via transmission of the gene encoding the enzyme/pro-pesticide system in a laboratory environment or a natural environment.

The application states on pages 13 to 14 that:

> According to the present invention, insects are generated which can be released into wild-type populations of insects. The

> transgenic insects of the invention will consequently interbreed with the wild-type populations to produce target insects which are susceptible to a proinsecticide. The invention thus relates to an insect of a given sex, which insect has been transformed with a gene comprising a coding sequence encoding one constituent of an enzyme/pro-drug system and a promoter capable of driving the coding sequence substantially only in insects of the opposite sex. Preferably, the insect is a male insect. Preferably the insect can be mass reared. More preferably, the insect is a Medfly.

The application also states on page 18 that:

> A highly susceptible strain is bred and male flies isolated. Introduction of male flies into a population of non-transgenic flies results in rapid transfer of the transgene. Female flies which are born inheriting the transgene are susceptible to 5-FC, whilst male files remain resistant.

In addition, factors to be considered when using the claimed method to control a large, wild-type population of insects in their natural habitats were well known in the art as of the filing date of the instant application. The Rule 1.132 Declaration of Dr. Charalambos Savakis and Dr. Roger K. Craig, filed herewith, establishes that the specification, in light of what is known in the art, clearly enables one of ordinary skill to practice the invention. Applicants submit via the Declaration submitted herewith, Exhibit A, a publication (Schliekelman and Gould, (2000) J. Econ. Entomology, 93(6); 1543-65) demonstrating the release of insects carrying a female killing or sterilization allele. The publication teaches the effectiveness of, and optimal strategies for, release of conditional lethal insects into a wild-type population.

In view of the above, Applicants submit that the claimed methods of controlling an insect population are properly enabled.

In the office action on page 5 the Examiner states, that "the instant invention appears to be unpredictable and undeveloped in light of Markaki et al" The Examiner asserts that, Markaki et al. teaches that the CD/5 FCYp1 promoter is unsuitable for large-scale applications due to delayed action, high cost of 5-FC, and observed sensitivity of non-transgenic males.

Applicants respectfully disagree with the Examiner. First, as argued above, the claims do not require that the methods be practiced in a large-scale application. Second, the Markaki et al. publication demonstrates the successful reduction to practice of the present invention by the inventors. For example, the publication states that, "the observation that relatively low concentrations of 5-FC (10 mM) can induce complete sterility in newly enclosed female transgenic flies suggests that CD produced in the fat body can readily demaniate 5-FC into 5-FU in amounts sufficient to kill dividing cells upon diffusion." (Column 2, p. 135) In addition, the publication states that the system "can be improved using other enzyme/pro-insecticide combinations." (Column 1, page 136) "There are a number of approved pro-insecticides whose selective activity in one species as opposed to another is dependent on the presence or absence of converting enzymes." (Column 1, page 136)

Third, although the Markaki et al. publication indicates the CD/5 FCYp1 promoter is unsuitable for large-scale applications, there is sufficient guidance in the application and knowledge within the art such that one could identify a suitable sex-specific regulatory element for use in large-scale applications without undue experimentation. The specification states on page 11 that:

> The conserved nature of yolk protein genes indicates that regulatory elements driving heterologous genes in female insects can be isolated and characterized using standard genetic approach..... In the case where the target insects are Medfly (*C. capitata*), the **VG1 and VG2 promoters** may be used as disclosed in Rina and Savakis, Genetics 127:769-80, 1991 herein incorporated by reference.

Furthermore, various structural features of sex-specific regulator elements are taught in the application which would allow one of ordinary skill to identify suitable sex-specific regulatory elements. The specification states on pages 11-12 that:

> A fat body enhancer (**FBE**) located 196 bp upstream of the Yp1 cap site **is sufficient to determine the sex-, stage- and fat body-specific expression of both yp1 and yp2 genes** as described by Garabedian et al. Cell 45:859-867, 1985, herein incorporated by reference. More recently, **a simple enhancer (33 bp) within the FBE has been postulated to be involved in the regulation of the yp gene expression**. This female- and fat body-specific enhancer consists of two enhancer elements (o and r). One

> element (22 bp) contains two protein binding sites, the dsx A and an overlapping bzip1, that binds the DmC/EBP (slbo) protein, a member of the bZIP family of transcriptional activators. The other element is an 11 bp binding site for an unknown protein (An and Wensink, 1995, EMBO J. 14:1221-1230).

In addition, other sex specific promoters that can be used in the present method are well known in the art. The Declaration by Dr. Charalambos Savakis and Dr. Roger K. Craig establishes that in view of the specification and further in view of what is known in the art, one of skill would predict that the claimed methods would be successful if performed with any of the sex-specific regulatory elements recited in the specification and/or described in the art. (See Exhibits B-F submitted herewith.)

The Examiner cites Komitopoulou (Exhibit F) as indicating that the HPS70 promoter in Drosophila is not efficient in other species. However, this publication also describes numerous sex specific promoters including the Yolk protein promoter, Chorion genes, Ceratoxin genes, as well as conditional promoters such as HSP70 that can be used in the methods of the present application. The publication teaches that six Medfly hsp70 genes have been identified with 84% identity at the amino acid level with D. melanogaster HSP70. The publication states on page 154 that "results indicate that the 263 bp upstream region of the Medfly hsp70 gene is sufficient for optimal promoter function at both normal and heat shock conditions."

In view of all of the above, Applicants respectfully request the Examiner withdraw the rejection to claims 1-14 and 21 are under 35 U.S.C. 112, first paragraph, enablement.

Written Description

The Examiner also rejected Claims 1-14 and 21 are under 35 U.S.C. 112, first paragraph, for allegedly failing to comply with the written description requirement. The Examiner stated at page 8:

> The nucleotide sequences that comprise sex-specific insect regulatory regions encompassed within the genus, for use in the claimed methods, have not been disclosed. The specification has disclosed use of the Yp1 promoter (sequence not disclosed), which was derived from Drosophila, but has not disclosed any other

> promoters for use in the claimed methods. . . .There is no evidence on the record of a relationship between the structures of any of the insect sex-specific regulatory regions that would provide any reliable information about the structure of regulatory regions within the genus. There is no evidence on the record that the Yp1 promoter had a known structural relationship to any other sex-specific insect regulatory region. In view of the above considerations one of skill in the art would not recognize that applicant was in possession of the necessary common features or attributes possessed by member of the genus of sex-specific insect regulatory regions, because the Drosophila Yp1 promoter is not representative of the claimed genus. Consequently, since Applicant was in possession of only the Drosophila Yp1 promoter and since the art recognized variation among the species of the genus of sex-specific insect regulatory regions, the Drosophila Yp1 promoter was not representative of the claimed genus.

Applicants note that the Examiner has stated that the Applicants were in possession of the Drosophila Yp1 promoter. Applicants disagree with the Examiner's assertion that the sequence of the Yp1 promoter was not disclosed. The specification states on page 5, that the "The *Xho*II *Bam*HI fragment containing the YP1 promoter/enhancer (from bases -362 to +54, Genbank Accession Number X01524) was obtained by PCR from *Drosophila* (strain *yw*) DNA." Thus, the nucleic acid sequence of the YP1 promoter/enhancer is identified based on Genbank Accession No. X01524.

Applicants also disagree with the Examiner's assertion that the specification has not disclosed any other promoters for use in the claimed methods, other than the YP1 promoter/enhancer derived from Drosophila. The specification teaches sex-specific promoters in Medflies. The specification also teaches that based on the conserved nature of sex-specific regulatory elements, one of skill can characterize hetrologous genes using standard genetic approaches. The specification teaches on page 11 that:

> Yolk protein genes have also been characterized for the Medfly (Rina and Savakin, 1991, Genetics 127:769-780). The conserved nature of yolk protein genes indicates that regulatory elements driving heterologous genes in female insects can be isolated and characterized using standard genetic approach..... In the case where the target insects are Medfly (*C. capitata*), the **VG1 and**

> **VG2 promoters** may be used as disclosed in Rina and Savakis, Genetics 127:769-80, 1991 herein incorporated by reference.

The specification also teaches that "sex-specific promoters suitable for driving a coding sequence as set forth above are available in the art." Examples of sex-specific promoters suitable for expression are described above. Applicants submit via the Declaration submitted herewith, Exhibits B-F, which described various sex-specific regulatory elements known in the art. Furthermore, structure based details of the YP1 promoter would enable one of ordinary skill to identify other promoters with methods known in the art. The specification teaches various YP1 structure elements. The application states on page 11:

> A fat body enhancer (**FBE**) located 196 bp upstream of the Yp1 cap site **is sufficient to determine the sex-, stage- and fat body-specific expression of both yp1 and yp2 genes** as described by Garabedian et al. Cell 45:859-867, 1985, herein incorporated by reference. More recently, **a simple enhancer (33 bp) within the FBE has been postulated to be involved in the regulation of the yp gene expression**. This female- and fat body-specific enhancer consists of two enhancer elements (o and r). One element (22 bp) contains two protein binding sites, the dsx A and an overlapping bzip1, that binds the DmC/EBP (slbo) protein, a member of the bZIP family of transcriptional activators. The other element is an 11 bp binding site for an unknown protein (An and Wensink, 1995, EMBO J. 14:1221-1230).

Thus, the combination of the teachings of the specification describing sex-specific regulatory elements, and knowledge in the art provides adequate written description for the genus of sex-specific regulatory elements. In view of the above, Applicants respectfully request reconsideration and withdrawal of the rejections of claims 1-14 and 21 under 35 U.S.C. 112, first paragraph, written description.

Applicants submit that all claims are allowable as written and respectfully request early favorable action by the Examiner. If the Examiner believes that a telephone conversation with Applicant's attorney/agent would expedite prosecution of this application, the Examiner is cordially invited to call the undersigned attorney/agent of record.

Respectfully submitted,

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